

## **DETAILED ACTION**

### ***Specification***

The instant specification is not in compliance with the sequence rules, 37 CFR 1.821-1.825. Figures 1 and 2 disclose sequences that are not included in the sequence listing. These sequences should be referenced by appropriate sequence identifiers in the specification or in the figure itself. Correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

SEQ ID NOS: 2 and 4 are disclosed as being novel fibulin-like polypeptides. The specification does not disclose any significant homology to any fibulin protein that has been disclosed and characterized in the prior art. A sequence search of SEQ ID NOS: 2 and 4 did not reveal any significant homology to any fibulin protein disclosed and characterized in the prior art. (See for example prior art to Argrave et al., Tran et al., and Pan et al. for fibulin-1.) Although Figure 2 aligns SEQ ID NO: 2 (designated SCS0007) with AK056571 (corresponding to SEQ ID NO: 2652 of Isogai et al., U.S. Patent No. 6,979,557), the protein of Isogai et al. itself is disclosed as being only weakly similar to fibulin-1, isoform A precursor. Isogai et al. does not

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determine any biological activity for this protein. The Genbank entry for XP\_166226 (see Figure 2) provides no citation or reference for the source of this sequence. No verified biological activity or use for this protein is provided. Searching Genbank for HCP50656.1 (see Figure 1) did not reveal a verified biological activity or use for this protein. FLJ32009 appears to correspond to a protein characterized by Lian et al. (2003). This reference was published **after** the priority date claimed by applicant. The protein disclosed by Lian et al. is not identified as a fibulin-like protein or as having calcium binding EGF domains. The alignment of SEQ ID NO: 2 to the sequences in Figure 1 shows significant sequence variation.

With respect to variants and fragments that bind calcium ions (see at least claims 57, 60, 61, 63, 66, and 67), the specification does not identify those amino acids or domains responsible for calcium binding activity. As such, one of ordinary skill in the art would not know which areas of SEQ ID NO: 2 or 4 could be mutated and retain this activity. In fact, the specification does not demonstrate that the full length sequences of SEQ ID NOS: 2 and 4 bind calcium ions themselves.

With respect to claim 62, the specification does not disclose the chemical structure of any peptide mimetics. The specification does not disclose the structure or function that must be present to meet the limitations of this claim. It is not known what biological activity is required by this claim.

With respect to claims 63-67, the specification does not provide any examples of administering SEQ ID NOS: 2 or 4 to any individual with the recited diseases or conditions and showing any positive effect. The specification and prior art of record do not disclose or establish that SEQ ID NOS: 2 or 4 or any fibulin-like protein can be used to treat any or all of the recited

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diseases or conditions. There are no proteins with established biological activities or comparable methods of treatment disclosed by which one of ordinary skill in the art would have been able to extrapolate to the claimed methods of treatment.

The specification does not establish a biological activity for SEQ ID NOS: 2 and 4. In the absence of such an activity, one of ordinary skill in the art would not have known how to use these proteins. The claimed methods of treatment are an invitation to experiment in view of the lack of guidance, absence of examples, and lack of knowledge in the prior art.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 57 and 60-62 are rejected under 35 U.S.C. 102(e) as being anticipated by Isogai et al. (U.S. Patent No. 6,979,557).

Isogai et al. discloses SEQ ID NO: 2652. This protein is disclosed as being related to fibulin-1 isoform A. See at least column 37, line 47; columns 121-124, particularly column 123, line 63; and column 213, lines 7-8. This protein has greater than 88% identity (i.e. no more than 15% of the amino acid residues in the sequence are changed) to instant SEQ ID NOS: 2 and 4. The polypeptide of Isogai et al. comprises fragments of SEQ ID NOS: 2 and 4. It can be considered a peptide mimetic as recited in claim 62. See sequence alignments set forth below.

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The instant application premises the activity of SEQ ID NOS: 2 and 4 based on the homology to the sequence of Isogai et al. See at least instant Figure 2.

The prior art attributes the calcium binding activity of fibulin to epidermal growth factor domains (EGF domains) 5-9. (See for example Tran et al.) The sequence of Isogai et al. contains sequence corresponding to some of these domains. Absent evidence to the contrary, the protein of Isogai et al. would bind calcium ions thereby meeting the limitations of the claims. Should applicant provide evidence that calcium ions are not bound by the sequence of Isogai et al. this will be considered further evidence that the claims are not enabled for fragments and variants that bind calcium ions.

Alignment of instant SEQ ID NO: 2 with SEQ ID NO: 2652

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US-10-094-749-2652
; Sequence 2652, Application US/10094749
; Patent No. 6979557
; GENERAL INFORMATION:
; APPLICANT: ISOGAI, TAKAO
; SEQ ID NO 2652
; LENGTH: 955
; TYPE: PRT
; ORGANISM: Homo sapiens
US-10-094-749-2652
```

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Query Match          88.3%; Score 4105; DB 2; Length 955;
Best Local Similarity 77.8%; Pred. No. 2.9e-239;
Matches 752; Conservative 6; Mismatches 28; Indels 180; Gaps
10;
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```
Qy          1 MWAGLLLRAACVALLLPGAPARGYTGRKPPGHFAAERRRLGPHVCLSGFGSGCCPGWAPS 60
|
Db          1 MWAGLLLRAACVALLLPGAPARGYTGRKPPGHFAAERRRLGPHVCLSGFGSGCCPGWAPS 60

Qy          61 MGGGHCTLPLCSFGCGSGICIAPNVCSCQDGEQGATCPETHGPCGEYGC DLTCNHGGCQE
120
|
Db          61 MGGGHCTLPLCSFGCGSGICIAPNVCSCQDGEQGATCPETHGPCGEYGC DLTCNHGGCQE
120

Qy          121 VARVCPVGFSMTETAVGIRCTDIDECVTSSCEGHCVNTEGGFVCECGPGMQLSADRHSCQ
180
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Db 121 VARVCPVGFMSMTEAAVGIRCTDIDECVTSSCEGHCVNTEGGFVCECGPMQLSADRHSCQ  
180

Qy 181 DTDECLGTPCQQRCKNSIGSYKCSRTGFHLHGNRHSCVDVNECRRPLERRVCHHSCHNT  
240

Db 181 DTDECLGTPCQQRCKNSIGSYKCSRTGFHLHGNRHSCVDVNECRRPLERRVCHHSCHNT  
240

Qy 241 VGSFLCTCRPGFRLRADRVSCG-----AL-----  
265

Db 241 VGSFLCTCRPGFRLRADRVSCFAFPKAVLAPSAILQPRQHPSKMLLLLPEAGRPALSPGH  
300

Qy 266 SPPDWQQGPLPAG-----TW-----  
280

Db 301 SPPSGAGGP-PAGVRTTRLPSPTPRLPTSSPSAPVWLLSTLLATPVPTASLLGNLRPPSL  
359

Qy 281 -----EPCMNQGVAGQSLG-----  
294

Db 360 LQGEVMGTPSSPRGPESPRLAAGPSPCWHLGAMHESRSRWTEPGCSQCWCEDGKVTCEKV  
419

Qy 295 -----VPSA-GARLETCRACF-----VSVLLA-----  
315

Db 420 RCEAACSHPIPSRDGGCCPCTGCFHSGVVRAEGDVFSPNENCTVCVCLAGNVSCISPE  
479

Qy 316 ----RVRPPIKTDCCCTCPVRCYFHGRWYADGAVFSGGGDECTTCVCQNGEVECSFMPCP  
371

Db 480 CPSPGPCQTPPQTDCCCTCPVRCYFHGRWYADGAVFSGGGDECTTCVCQNGEVECSFMPCP  
539

Qy 372 ELACPREEWRLGPGQCCFTCQEPTPSTGCSLDDNGVEFPIGQIWSPGDPCELCICQADGS  
431

Db 540 ELACPREEWRLGPGQCCFTCQEPTPSTGCSLDDNGVEFPIGQIWSPGDPCELCICQADGS  
599

Qy 432 VSCKRTDCVDSCPHPIRIPGQCCPDCSAAGAQRMLSLAGCTYTGRIFYNNETFPSVLDPC  
491

Db 600 VSCKRTDCVDSCPHPIRIPGQCCPDCS-----AGCTYTGRIFYNNETFPSVLDPC  
649

Qy 492 LSCICLLGSVACSPVDCPITCTYFHPDGECCPVCRCDCNYEGRKVANGQVFTLDDEPCTR  
551

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      |||
Db      650 LSCICLLGSVACSPVDCPITCTYPFHPDGECCPVCRCDCNYEGRKVANGQVFTLDDEPCTR
709
      |||
Qy      552 CTCQLGEVSCEKVPCQRACADPALLPGDCCSSCPDSLSPLEEKQGLSPHGNVAFSKAGRS
611
      |||
Db      710 CTCQLGEVSCEKVPCQRACADPALLPGDCCSSCPDSLSPLEEKQGLSPHGNVAFSKAGRS
769
      |||
Qy      612 LHGDTEAPVNCSSCPGPPTASPSRPVLHLLQLLLRTNLMKTQTLPTSPAGAHGPHSLALG
671
      |||
Db      770 LHGDTEAPVNCSSCPGPPTASPSRPVLHLLQLLLRTNLMKTQTLPTSPAGAHGPHSLALG
829
      |||
Qy      672 LTATFPGEPEGASPRLSPGPSTPPGAPTLPLASPGAPQPPPVTPEFSASGAQIVSRWPP
731
      |||
Db      830 LTATFPGEPEGASPRLSPGPSTPPGAPTLPLASPGAPQPPPVTPEFSASGAQIVSRWPP
889
      |||
Qy      732 LPGTLLTEASALSMMDPSPSKTPITLLGPRVLSPTTSRLSTALAATTHPGPQQPPVGASR
791
      |||
Db      890 LPGTLLTEASALSMMDPSPSKTPITLLGPRVLSPTTSRLSTALAATTHPGPQQPPVGASR
949
      |||
Qy      792 GEESTM 797
      |||
Db      950 GEESTM 955
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Alignment of instant SEQ ID NO: 4 with SEQ ID NO: 2652

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US-10-094-749-2652
; Sequence 2652, Application US/10094749
; Patent No. 6979557
; GENERAL INFORMATION:
; APPLICANT: ISOGAI, TAKAO
; LENGTH: 955
; TYPE: PRT
; ORGANISM: Homo sapiens
US-10-094-749-2652
```

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Query Match          88.1%; Score 4001; DB 2; Length 955;
Best Local Similarity 77.4%; Pred. No. 9.2e-233;
Matches 732; Conservative 6; Mismatches 28; Indels 180; Gaps
10;
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Qy      1 ARGYTGRKPPGHFAAERRRLGPHVCLSGFGSGCCPGWAPSMGGGHCTLPLCSFGCGSGIC 60
      |||
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Db 21 ARGYTGRKPPGHFAAERRRLGPHVCLSGFGSGCCPGWAPSMGGGHCTLPLCSFGCGSGIC 80

Qy 61 IAPNVCSCQDGEQGATCPETHGPCGEYGCDLTCNHGGCQEVARVCPVGFSMTETAVGIRC  
120

Db 81 IAPNVCSCQDGEQGATCPETHGPCGEYGCDLTCNHGGCQEVARVCPVGFSMTEAAVGIRC  
140

Qy 121 TDIDECVTSSCEGHCVNTEGGFVCECGPGMQLSADRHSCQDTDECLGTPCQQRCKNSIGS  
180

Db 141 TDIDECVTSSCEGHCVNTEGGFVCECGPGMQLSADRHSCQDTDECLGTPCQQRCKNSIGS  
200

Qy 181 YKCSCRTGFHLHGHRHSCVDVNECRRPLERRVCHHSCHNTVGSFLCTCRPGFRLRADRV  
240

Db 201 YKCSCRTGFHLHGHRHSCVDVNECRRPLERRVCHHSCHNTVGSFLCTCRPGFRLRADRV  
260

Qy 241 CEG-----AL----SPPDWQQGPLPAG-----  
258

Db 261 CEAFPKAVLAPSAILQPRQHPSKMLLLLPEAGRPALSPGHSPPSGAPGP-PAGVRTTRL  
319

Qy 259 -----TW-----  
260

Db 320 SPTPRLPTSSPSAPVWLLSTLLATPVPTASLLGNLRPPSLLQGEVMGTPSSPRGPESPL  
379

Qy 261 ----EPCMNQGVAGQSLG-----VPSA-GARLET  
284

Db 380 AAGPSPCWHLGAMHESRSRWTEPGCSQCWCEDGKVTCEKVRCEAACSHPIPSRDGGCCPS  
439

Qy 285 CRACF-----VSVLLA-----RVRPPIKTDCTCVPV  
311

Db 440 CTGCFHSGVVRAEGDVFSPNENCTVCVCLAGNVSCISPECPSGPCQTTPQTDCTCVPV  
499

Qy 312 RCFYHGRWYADGAVFSGGGDECTTCVCQNGEVECSFMPCPELACPREEWRLGPGQCCFTC  
371

Db 500 RCFYHGRWYADGAVFSGGGDECTTCVCQNGEVECSFMPCPELACPREEWRLGPGQCCFTC  
559

Qy 372 QEPTPSTGCSLDDNGVEFPIQIWSPGDPCELCICQADGSVSKRTDCVDSCPHPIRIPG  
431

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Db 560 QEPTSTGCSLDDNGVEFPIQIWSPGDPCELCICQADGSVSCKRTDCVDSCPHPIRIPG  
619

Qy 432 QCCPDCSAAGAQRMLSLAGCTYTGRIFYNNETFPSVLDPCLSCICLLGSVACSPVDCPIT  
491

Db 620 QCCPDCS-----AGCTYTGRIFYNNETFPSVLDPCLSCICLLGSVACSPVDCPIT  
669

Qy 492 CTYPFHPDGECCPVCRCDCNYEGRKVANGQVFTLDDEPCTRCTCQLGEVSCEKVPCQRACA  
551

Db 670 CTYPFHPDGECCPVCRCDCNYEGRKVANGQVFTLDDEPCTRCTCQLGEVSCEKVPCQRACA  
729

Qy 552 DPALLPGDCCSSCPDLSPLEEKQGLSPHGNVAFSKAGRSLHGDTEAPVNCSSCPGPPTA  
611

Db 730 DPALLPGDCCSSCPDLSPLEEKQGLSPHGNVAFSKAGRSLHGDTEAPVNCSSCPGPPTA  
789

Qy 612 SPSRPVLHLLQLLLRTNLMKTQTLPTSPAGAHGPHSLALGLTATFPGEPEGASRLSPGPS  
671

Db 790 SPSRPVLHLLQLLLRTNLMKTQTLPTSPAGAHGPHSLALGLTATFPGEPEGASRLSPGPS  
849

Qy 672 TPPGAPTLPLASPGAPQPPPVTPEFSASGAQIVSRWPPLPGTLLTEASALSMDPSPS  
731

Db 850 TPPGAPTLPLASPGAPQPPPVTPEFSASGAQIVSRWPPLPGTLLTEASALSMDPSPS  
909

Qy 732 KTPITLLGPRVLSPTTSRLSTALAATTHPGPQQPPVGASRGEESTM 777  
777

Db 910 KTPITLLGPRVLSPTTSRLSTALAATTHPGPQQPPVGASRGEESTM 955  
955

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various



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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 63 and 66-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isogai et al. (U.S. Patent No. 6,979,557) in view of Godbole et al. (US Patent Publication 2003/0100746).

Isogai et al. is applied as above but does not disclose methods of treatment.

Godbole et al. discloses using fibulin proteins to promote bone and cartilage regeneration in methods of treatment. See at least pages 22 and 25.

It would have been obvious to use the fibulin protein of Isogai et al. in the method of treatment disclosed by Godbole et al. One would have been motivated to do so to provide additional therapies to treat these conditions.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (571)272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/  
Primary Examiner, Art Unit 1647

mpa